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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/641,892	08/18/2000	Hiroshi Izui	195942US0	6721

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EXAMINER

LAMBERTSON, DAVID A

ART UNIT	PAPER NUMBER
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1636

DATE MAILED: 03/26/2003

92

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/641,892

Applicant(s)

IZUI ET AL.

Examiner

David A. Lambertson

Art Unit

1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10 January 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-24 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-24 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 10 January 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

Art Unit: 1636

DETAILED ACTION

Receipt is acknowledged of a reply, filed January 10, 2003 as Paper No. 21, to the previous Office Action. Amendments were made to the claims. Specifically, new claims 14-24 were added.

Claims 1-24 are pending and under consideration in the instant application. Any rejection of record in the previous Office Action, Paper No. 18, mailed September 13, 2002, that is not addressed in this action has been withdrawn.

Drawings

The drawings have been accepted by the draftsperson.

Specification

A substitute specification in proper idiomatic English and in compliance with 37 CFR 1.52(a) and (b) is required. The substitute specification filed must be accompanied by a statement that it contains no new matter.

For example, the sentence bridging pages 2-3 reads, "There is known a method wherein fermentation is performed with crystallizing L-amino acid accumulated in culture." This sentence is clearly not in the proper English vernacular. The instant specification is replete with such errors, and this is simply an example.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

Art Unit: 1636

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 10, 14 and 17-21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant claims *any* microorganism with the ability to produce L-glutamic acid in a medium comprising L-glutamic acid at the saturation concentration, where the L-glutamic acid accumulates past the saturation point of the medium. The claims read on a broad genus of microorganisms that have this function, and the use of these microorganisms to produce L-glutamic acid.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics sufficient to show applicants were in possession of the claimed genus. In the instant case, the specification does not sufficiently describe a representative number of species by actual reduction to practice.

Applicant claims a microorganism with the ability to produce L-glutamic acid in a medium comprising L-glutamic acid at the saturation concentration, where the L-glutamic acid accumulates past the saturation point of the medium, by function only, without any disclosed or known correlation between the elements and their function. The specification only provides

Art Unit: 1636

teachings regarding a specific microorganism, *Enterobacter agglomerans*, and its ability to produce L-glutamic acid in a medium comprising L-glutamic acid at the saturation concentration, where the L-glutamic acid accumulates past the saturation point of the medium. Aside from the *Enterobacter agglomerans*, the specification does not teach any microorganism that can be isolated in order to have the ability to produce L-glutamic acid in a medium comprising L-glutamic acid at the saturation concentration, where the L-glutamic acid accumulates past the saturation point of the medium. The description of a single type of microorganism is not deemed to be descriptive of a reasonable representation of all microorganisms, therefore the skilled artisan cannot envision a sufficient number of embodiments of the instant invention from the instant specification.

The prior art does not provide sufficient information on the subject to overcome the deficiencies of the instant specification. There is no description in the prior art that allows one to envision a representative number of microorganisms that can produce glutamic acid in medium where glutamic acid is at its saturation point so that one of skill in the art could identify and use said microorganisms in the instant invention. Thus the skilled artisan cannot rely on the prior art to envision a sufficient number of embodiments of the instant invention to see that the applicant was in possession of the claimed genus.

Neither the specification of the instant application or the prior art teaches a structure-function relationship for a representative number of microorganisms that can produce glutamic acid in medium where glutamic acid is at saturation. Applicant's present no teachings on the metabolic pathways, gene mutations, etc., which enable the *E. agglomerans* strain to produce L-glutamic acid under the recited conditions in terms of how they would be reproducible in other

Art Unit: 1636

microorganisms. As a result, the skilled artisan would not be able to envision the claimed invention by relying on the teachings of the prior art or the instant specification. Therefore applicant has not satisfied the written description requirement to show the skilled artisan that they were in possession of the claimed genus.

Claims 4-6 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant's invention is any microorganism that can survive at a low pH, in the presence of a saturating concentration of L-glutamic acid, and produce L-glutamic acid even at the already high concentration present in the medium. In some embodiments, the microorganism is further genetically engineered for favorable production of L-glutamic acid. The invention is also drawn to methods of producing L-glutamic acid using these microorganisms, and methods of isolating the microorganisms.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following:

Art Unit: 1636

Nature of the invention. The nature of the invention involves the genetic engineering of microorganisms to increase or decrease the expression of different enzymes that are involved in the biosynthesis of L-glutamic acid. This requires the knowledge of all pathways involved in L-glutamic acid synthesis in all microorganisms.

Scope of the invention. The scope of the invention is extremely broad, encompassing microorganisms, many of which are not even minutely characterized with respect to L-glutamic acid production.

State of the art. The state of the art as it regards metabolic engineering of all microorganisms is very unpredictable. Support for this assertion comes from the teachings of Bailey (Science 252: 1666-1675, 1991). Bailey indicates that, "At the present, metabolic engineering is more a collection of examples than a codified science" (see for example page 1668, third paragraph, left side), suggesting that a single example of successful metabolic engineering does not indicate that the same principles or methods used in the single example are adequate to define any other situation. This is further supported by the indication that "many studies have shown the feasibility of metabolic engineering methods without achieving the yields rates or titers required for a practical process" (see for example page 1668, third paragraph, left side). Furthermore, "the route of reactions to a desired product passes several forks where intermediates can enter alternative pathways..." and "Maximizing product formation requires that the desired route at each fork be made a priority and that traffic in alternative pathways be minimized to the extent possible without decreasing cell viability" (see page 1671, second full paragraph, right side). In this particular instance, the invention requires knowledge of a vast number of species, including what each of the enzymes for the desired activities are, whether their overexpression/deletion/etc.

Art Unit: 1636

can be achieved with the desired yield of producing more L-glutamic acid than that which is present in the medium, to what level can these enzymes be modified without compromising the viability of the strain, how these biosynthetic pathways operate, etc. The prior art does not teach such a vast amount of information so that the skilled artisan, seeking to isolate any microorganism with the ability to produce L-glutamic acid in a medium that is already at saturation for L-glutamic acid, would be able to consult the prior art so that such a microorganism can be produced. Similarly, it would be impossible to predictably engineer every microorganism to increase the activity of an L-glutamic acid biosynthesis enzyme, or decrease the activity of a branch point enzyme, wherein such enzymes have not been adequately characterized. As a result, the skilled artisan could not turn to the prior art in order to make and use the invention as claimed without performing unpredictable trial and error experimentation.

Number of working examples and Guidance provided by applicant. Applicant only provides a single working example regarding the isolation of *Enterobacter agglomerans*, and its modification along the pathways of L-glutamic acid biosynthesis. This is not indicative of an ability to predictably practice the invention with regard to all microorganisms. The skilled artisan could not consult the instant specification on how to genetically engineer any other microorganism to produce L-glutamic acid in a medium that is already at saturation for L-glutamic acid, by modifying the biosynthetic pathway for L-glutamic acid in that organism.

Level of skill in the art. The level of skill in the art is highly underdeveloped. L-glutamic acid production is not well characterized in a wide array of microorganisms, and has generally been limited to Coryneform bacteria. There are a vast number of microorganisms for which citrate synthase or glutamate dehydrogenase or α -ketoglutaric dehydrogenase have not been identified

Art Unit: 1636

or characterized in such a manner that these enzymes can be modulated to suit the requirements of the instant claims. In addition, there are many variables, such as a microorganism's ability to survive in a low pH environment, the effects of feedback inhibition on a microorganism, etc., that are not addressed in either the prior art or the instant specification.

Unpredictability of the art. The art is highly unpredictable. As set forth by the teachings of Bailey, the metabolic engineering of one organism does not equate to an ability to perform such modifications in another organism. To quote Bailey, "Further improvements in rates of amino acid synthesis and yields...depend on a better understanding of mechanisms of gene regulation and metabolite flow" (see for example page 1672, first incomplete paragraph, left side). Unless these pathways are understood in every organism, the skilled artisan cannot make or use the invention commensurate with the scope of the claims without practicing undue and unpredictable trial and error experimentation. Such experimentation would include, identifying an organism that does not have a prevalent feedback mechanism for L-glutamic acid, identifying and characterizing the entire pathway for L-glutamic acid biosynthesis for each microorganism and obtaining information regarding the level of modulation that can be achieved in the microorganism (with regard to L-glutamic acid production) without compromising the viability of the microorganism.

Amount of experimentation. The invention as claimed entails an enormous amount of experimentation, including the biochemical characterization of L-glutamic acid biosynthesis in millions of microorganisms and understanding the level of modification that can be performed on any particular microorganism without affecting the organism's viability. The amount of experimentation is undue and unpredictable because the skilled artisan would not know whether

Art Unit: 1636

or not there was a reasonable expectation of success in modifying any particular microorganism to produce L-glutamic acid in a medium where L-glutamic acid was already at a saturated level.

As such, the claimed invention is not enabled for the entire scope of the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-10, 14 and 17-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the claims recite the limitation "has the ability to accumulate L-glutamic acid in an amount exceeding the amount corresponding to the saturation concentration in the liquid medium at the specific pH." This is indefinite because it is unclear whether the L-glutamic acid is being accumulated in the microorganism, or if the glutamic acid is being excreted by the organism into the medium so that the concentration of the medium exceeds the saturation point.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 10-13 and 15-24 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 5-8 of copending Application No. 10/077,751 (also PG PUB US 2002/0192772; henceforth '751). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application are genus claims that are anticipated by the specific claims of '751. Specifically, the instant claims are anticipated by the more narrowly defined claims of '751 which further indicate that the pH be 5.0 or less *and* where the growth of the organism is not inhibited.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 10-13 and 15-24 are directed to an invention not patentably distinct from claims 1 and 5-8 of commonly assigned Application No. 10/077,751. Specifically, the claims of the instant application are genus claims that are anticipated by the specific claims of '751. Specifically, the instant claims are anticipated by the more narrowly defined claims of '751 which further indicate that the pH be 5.0 or less *and* where the growth of the organism is not inhibited.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned 10/077,751, discussed above, would form the basis for a rejection of the

Art Unit: 1636

claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 37 CFR 1.78(c) and 35 U.S.C. 132 to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

Allowable Subject Matter

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Lambertson whose telephone number is (703) 308-8365. The examiner can normally be reached on 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Art Unit: 1636

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

David A. Lambertson
March 21, 2003

DAVID GUZO
PRIMARY EXAMINER
David Guzo